

REMARKS/ARGUMENTS

Responsive to the Office Action of August 29, 2007.

Reconsideration is requested in light of the clarification which follows.

Claim 140 has now been revised per the Examiner's comments in the Office Action at paragraph 11. Claim 140 is now free of rejection. Claim 140 now is seen to be allowable.

Claim 142 stands allowed. Claim 141 differs from claim 142 only in that in claim 141 the capsid sequence can, as known in the art, vary in minor respects.

The pending claims are 140 to 144, 146 and 147.

Claim 141 was rejected under 35 U.S.C. 112, second paragraph, Office Action paragraph 10. By the above amendment claim 141 has been modified to closely track the form of allowed claim 142. Claim 140, like claim 142, is now clear in the recitation of the steps of the method. The rejection under 35 U.S.C. 112 should be withdrawn.

Paragraphs 13 and 14 of the Office Action do not require a response. However it is pointed out that neither Houghton United States Patent No. 5,350,671 nor Wang United States Patent No. 5,436,126 disclose any complete capsid antigen as an isolate, as is discussed below.

The rejection on Houghton United States Patent No. 5,350,671 ('671), Office Action, paragraph 17, based on alleged obviousness, 35 U.S.C. 103(a), should be withdrawn. Generic claim 141 is to the use of combined capsid and C-100-3 antigens in a method for the early detection of HCV. At a late stage following NANBV infection, the antibodies in a sample do not necessarily react with the capsid antigen, see Substitute Specification, page 104, Table 5, chimp 10, week 51 where there was no reaction with the capsid. The capsid detects early seroconversion. These results as disclosed in the present patent application revealed for the first time the important benefit to be derived from using capsid antigen for the detection of HCV seroconversion at early times after infection in conjunction with the C100-3 antigen ("Anti HCV" in Table 5). The individual patient does not present as "early" or "late" infected. Thus, each antigen contributes to an overall major benefit in the detection of a wide range of HCV infections, both early and late. This represented the solution to a serious problem particularly occurring at an early stage after infection, viz., the reduction in the incidence of non-detection of HCV seroconversion, that is, the problem of false negatives early after infection.

The Examiner acknowledges that Houghton does not disclose the combination of capsid and C-100-3 antigens. Thus, it follows that the subject matter of claim 141 is not “inherent” in Houghton. Houghton does not disclose the use of the two antigens or the detection of seroconversion at early times after infection with any antigen.

“Obviousness cannot be predicated on what is not known at the time the invention is made, even if the inherency of a certain feature is later established, In re Riukaert, 9 F3d 1531, 28 USPQ 2d 1955 (CAFC 1993)”, per MPEP 2141.02, p. 2100-125.

Riukaert is dispositive of the inherency issue in this case, see Riukaert at p. 1957, 28 USPQ 2d:

‘The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient [to establish inherency.]’ In re Oelrich, 666 F.2d 578# 581-82, 212 USPQ 323, 326 (CCPA 1981) (citations omitted) (emphasis added). ‘That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown.’ In re Spormann, 363 F.2d 444, 448, 150 USPQ 449, 452 (CCPA 1996). Such a retrospective view of inherency is not a substitute for some teaching or suggestions supporting an obviousness rejection. See In re Newell, 891 F.2d 899, 901, 13 USPQ2d 1248, 1250 (Fed. Cir. 1989).

The single reference in Houghton to the immunologic reactivity of antigens containing HCV epitopes reads as follows, ‘671, column 83, lines 16 to 53:

As seen from the results shown in FIG. 65, a number of clones expressed polypeptides containing HCV epitopes which were immunologically reactive with serum from individuals with NANBH. Five of these polypeptides were very immunogenic in that antibodies to HCV epitopes in these polypeptides were detected in many different patient sera. The clones encoding these polypeptides, and the location of the polypeptide in the putative HCV polyprotein (wherein the amino acid numbers begin with the putative initiator codon) are the following: clone 5-1-1; amino acids 1694-1735; clone C100, amino acids 1569-1931; clone 33c, amino acids 1192-1457; clone CA279a, amino acids 1-84; and clone CA290a amino acids 9-177. The location of the immunogenic polypeptides within the putative HCV polyprotein are shown immediately below.

| Clones encoding polypeptides of proven reactivity with sera from NANBH patients. |   | 3 <sup>1</sup> |
|--|---|----------------|
| Clone  | Location within the HCV polyprotein (amino acid no. beginning with putative initiator methionine) |                |
| CA279a   | 1-84  |                |
| CA74a  | 437-582   | 4 <sup>1</sup> |
| 13i  | 511-690   |                |
| CA290a   | 9-177   |                |
| 33c  | 1192-1457   |                |
| 40b  | 1266-1428   |                |
| 5-1-1  | 1694-1735   |                |
| 81   | 1689-1805   | 4 <sup>1</sup> |
| 33b  | 1916-2021   |                |
| 25e  | 1949-2124   |                |
| 14c  | 2054-2223   |                |
| 8f   | 2200-3325   |                |
| 33f  | 2287-2385   |                |
| 33g  | 2348-2464   | 5 <sup>1</sup> |
| 39c  | 2371-2502   |                |
| 15e  | 2796-2886   |                |
| C100   | 1569-1931   |                |

Figure 65 presents the antigenicity of polypeptides expressed from HCV cDNA clones used in an antigenic mapping study of the putative HCV polyprotein, '671, column 11, lines 1 et. seq. Of the polypeptides of Figure 65, the seventeen (17) listed above were identified by Houghton as immunologically reactive with sera from individuals already known to be NANBV positive. Specifically, in the Table of Figure 65, Houghton lists what appears to be a series of samples of a "Chronic HCV Patient C100 positive" which shows that the only two core antigens, identified as CA 279a (identified, presumably incorrectly, as "CA 259a" in '671 Figure 65) and CA 290a, which Houghton discloses, score as reactive only with samples no. 5-8, not the first four samples of the C100 positive panel. In contrast, clone 5-1-1 (the latter constituting a part of the C100 antigen, see Houghton, Figure 69) as well as C-100-3 itself both score as reactive with all these eight specimens. Similarly, in the leftmost columns of Figure 65, Houghton presents three serum specimens as "1. Post acute", "2. Post acute" and "3. C100 Conversion" respectively. None of these score as reactive with his capsid antigens

There is nothing in the actual data of Houghton, summarized above, to suggest that any of his seventeen (17) antigens, when contacted with sera obtained at early times after infection, would score as reactive.

Houghton also fails to distinctly identify and point out the problem associated with serology based on the C-100-3 antigen in that the later antigen is not associated with detection of antibodies to HCV at early times after infection. The lack of

acknowledgment of the problem inevitably leads to a failure to provide the solution to this problem, namely the provision of a method for detection at early times after infection (which method incorporates providing the capsid antigen encoded by HCV recited in claim 141). In fact, Houghton teaches away from the solution by merely disclosing that several of the seventeen (17) antigens were "very immunogenic", thus failing to discriminate between or recognize their distinct properties. In contrast, the instant application clearly presents the problem, and its solution.

The term "very immunogenic" as used by Houghton is meaningless in the context of the detection of early seroconversion since Houghton's serum samples were from patients already known to be seropositive and his grading of the reactivity of the seventeen (17) antigens with these serum samples could not reveal anything about when seroconversion took place. In Houghton '671, there is no discrimination between the five antigens provided as they are merely stated to be "very immunogenic", all similar. The present invention demonstrates they are not similar. More significantly, since Houghton never discloses that any of the seventeen (17) antigens detected early seroconversion, that is no teaching that any of the myriad possible combinations of the antigens would detect early seroconversion.

The Examiner acknowledges that Houghton does not teach the combined use of capsid with C-100-3 antigen. Further, as discussed above, Houghton never had any early sera which were tested with capsid and did not teach that the capsid was uniquely

effective in detecting early seroconversion and did not teach any way of minimizing the failure to detect early HCV infection. See also Section IV I1b, '671, column 120, lines 36 to 39 of Houghton, which appears to say that C-100-3 did not detect early seroconversion in chimps. In summary, if the problem presented were early detection, one skilled in the art would not expect any of the other sixteen antigens to be better than C-100-3 in detecting early seroconversion, nor would one expect any combination of the seventeen to detect early seroconversion.

While Houghton presents seventeen antigens of which five are "very immunogenic" antigens which he disclosed can be used in panels, he does not show any combinations and numerous combinations of the seventeen are possible (pairs, triplets, etc.). Therefore it is unreasonable to conclude that all of the hundreds and thousands of combinations were obvious given the large number of possible combinations, especially since Houghton provides no reason to expect that any combination will detect early seroconversion and reduce the incidence of false negatives.

The Supreme Court's latest word on obviousness and combination inventions is found in KSR International Co. v. Teleflex, Inc., 127 S.Ct. 1727, 82 USPQ 2d 1385 (2007). KSR clearly requires a common sense approach to assessing the obviousness of "combination" inventions. In KSR, the Court did not totally reject the Federal Circuit's teaching, suggestion or motivation (TSM) test - only a "rigid" approach to that

test. It acknowledged that most inventions are combinations of prior art elements. It indicated that the “teaching, suggestion or motivation” test had “no doubt” been applied in accordance with Supreme Court precedent “in many cases.”

In KSR the Court noted that the TSM requirement was first established in In re Bergel, 292 F.2d 955, 956-57 (CCPA 1961). The Court acknowledged that a requirement that a “teaching, suggestion, or motivation to combine known elements” be demonstrated to show that a combination of prior art elements is obvious “captured an helpful insight.” Common sense dictates that a patent claim to “a combination of two known devices” be looked at with care, but it “can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements” as in the claim. Most inventions are combinations of what is known.

The Court noted that the Federal Circuit itself, in decisions rendered while KSR was pending before the Court, had cautioned against rigid approaches and had emphasized that there is no requirement of an explicit suggestion to combine. Most notable is Chief Judge Michel’s opinion in Dystar Textilfarben GMBH & Co. Deutschland KG v. C. H. Patrick Co., 464 F.3d 1356 (Fed. Cir. 2006). In KSR, the Supreme Court quotes the Dystar statement: “Our suggestion test is in actuality quite flexible and not only permits, but requires, consideration of common knowledge and common sense.” The Court also quoted Alza Corp. v. Mylan Labs, Inc., 464 F.3d 1286, 1291 (2006) as follows: “There is flexibility in our obviousness jurisprudence because a

motivation may be found implicitly in the prior art. We do not have a rigid test that requires an actual teaching to combine..."

The Federal Circuit has linked to its TSM test a further requirement: there must have been "a reasonable expectation of success" in making an invention consisting of a combination of prior art elements. This might be called the TSM+ (plus) test.

In KSR, the Supreme Court did not disturb the expectation of success concept, and in fact, appears to have agreed with it. At one point, the patent owner in KSR argued that the prior art elements "cannot be combined" as in the patent claim in question. The Supreme Court held that this argument had not been raised in the lower courts "in a clear fashion," but it appeared to assume that evidence of difficulties or unpredictability in combining prior art teachings might render a combination non-obvious. The present claim 141 is allowable under the TSM+ test since Houghton merely discloses an array of polypeptides from HCV and never recognized the difficulty of isolating the specific ones which would provide early detection of HCV seroconversion. Houghton does not disclose any guidance in this area and hence applicants' discovery of a method which does detect early seroconversion and reduce false negatives was completely unpredictable.

Under Graham v. John Deere, 383 US 1, 148 USPQ 459 (1966), United States v. Adams, 383 US 39, 148 USPQ 479 (1966) and Federal Circuit law, so-called “secondary considerations” or “objective evidence”, such as a patented invention’s commercial success, long felt but unresolved need, failure of others, etc., frequently play a role in obviousness determinations. These considerations were considered by the Supreme Court in KSR to have continuing relevance. It noted that Graham “invited courts, where appropriate, to look at any secondary considerations that would prove instructive.”

As the Examiner notes, prior to the present invention it was known that C-100-3 did not detect all cases of seroconversion caused by HCV, Weiner et al, Lancet, 355:1-3, of record. The known inadequacy of C-100-3 in the detection of some cases of seroconversion actually serves to highlight the problem solved by the present invention. This evidence of a felt need and the failure of others to satisfy that need are significant evidence of non-obviousness, Graham v. John Deere, supra.

The rejections on Houghton '671 should be withdrawn.

Claim 141 cannot properly be rejected on Wang United States Patent No. 5,436,126 ('126) in view of Houghton under 35 U.S.C. 103(a), Office Action paragraph 18, since Wang does not claim the combination of capsid and C-100-3. The Examiner acknowledges in the Office Action, paragraph 14, that even though Wang is not prior art

as that term is normally understood in light of the Declaration Under 37 CFR 1.131, reliance on Wang is nevertheless proper because the Wang patent and the instant patent application claim “the same invention”. Claim 141 is clearly drawn to an invention which Wang did not claim (and could not have claimed). Wang did not claim detection of HCV using the capsid antigen with C-100-3 antigen. Wang is not “prior art” in any relevant respect. Wang does not teach the use of C-100-3 antigen with capsid antigen. In light of the Declaration Under 37 CFR 1.131 swearing back of Wang, the ‘126 patent is not prior art and the rejection on Wang in light of Houghton fails.

Arguendo, leaving aside the Declaration Under 37 CFR 1.131, the rejection also fails. As the Examiner has noted, neither Houghton nor Wang teach the use of the C-100-3 peptide with a capsid antigen. Consequently, the joint teachings of Wang and Houghton could not in any event be combined in any obvious manner to yield the subject matter of any of the claims.

Neither patent teaches the unique benefit of the combination of the two antigens, capsid and C-100-3, to minimize the risk of failure to detect HCV infection.

The Wang patent refers to “HCV C-100”. However, the peptide sequences shown from the C-100 region in the Wang patent, which are designated therein as I, II, III, IV, V and VI, Wang, column 18, lines 52 *et. seq.*, are each short sequences of about 40 amino acids which span Wang’s preferred immunodominant region of 90 amino

acids.

Wang peptide VII (aa 1889 to 1931), in column 17, is only a short sequence of 40 amino acids at the end of the 363 amino acid sequence of C-100-3 antigen. Wang does not disclose or suggest any combination of C-100-3 antigen (containing 363 amino acids, over four times as long as Wang's immunodominant region), with the capsid antigen in any EIA.

Wang '126 discloses the following HCV assay formats:

Format A - Peptides II H and V (column 15, lines 26 to 27);

Format B - Peptides II F, III D and V (column 14, lines 47 to 48);

Format C - Peptides II H, V and VIII E (column 15, lines 24 to 25); and

Format D - Peptides VIII E and IX D (column 15, lines 25 to 26).

None of these formats of Wang contains C-100-3 which is the antigen for late stage detection of infection. The capsid, as noted above, does not necessarily detect late stage, but is necessary to detect early infection. Consequently, the unique combination of C-100-3 and capsid according to claim 141 is not suggested by Wang.

Taking Houghton and Wang together, assuming the propriety of such combination of references which differ from each other in numerous significant respects, there simply is no basis for concluding that the subject matter of claim 141 was obvious therefrom.

For these additional reasons, the rejection on Wang with Houghton must be withdrawn.

The rejection on Wang in view of Houghton must be withdrawn for still other reasons.

The Wang patent was filed on July 26, 1990 under United States Patent Application Serial No. 07/558,799, copy of United States Patent and Trademark Office file history is included in the Declaration of Joseph E. Mueth, filed January 31, 2007. Applicants' effective filing date was August 27, 1990.

Leaving aside the Declaration Under 37 CFR 1.131, Wang could be relied upon under 35 U.S.C. 102(e) only for what it disclosed as of July 26, 1990.

The Examiner has cited to Wang Examples 17 and 18, and also to Wang claim 1.

The originally filed Specification of Wang, United States Patent Application Serial No. 07/558,799 ("Wang Specification") is found in the Declaration of Joseph E. Mueth, filed January 31, 2007.

The Wang Specification shows these pages as they read as of filing on July 26, 1990. Page 73, lines 11 to 21 read:

(c) Serial samples from three well-characterized representative HCV seroconversion panels, collected by Serologic Inc., were tested by HCV EIA formats A, C and D, as defined in Example 15 in addition to that previously tested with rDNA HCV C-100 based EIA. As shown in Table 8, both HCV EIA formats C and D were able to identify HCV antibody positive specimens in two out of three panels by four to eight weeks earlier than the rDNA HCV-100 based EIA and HCV EIA Format A. This further demonstrates the sensitivity of the HCV EIAs which incorporate peptides derived from the HCV structural (core) protein region.

The A, C and D formats, referred to in the above passage, are described in the Wang Specification at page 70, lines 1 to 18.

However, the Wang Specification as filed was replete with fatal sequence errors to which we now turn.

On January 31, 2007, we filed 24 pages of the original Wang Specification with all the changes marked, and in accordance with the Preliminary Amendment filed by Wang on December 10, 1990 (subsequent to applicants' filing date of August 27, 1990). These changes, which were enumerated sequentially (1 to 50), are indicated by the number written in the right margin of each page, and with an arrow pointing to the change.

The Wang patent application as filed on July 26, 1990 did not correctly disclose the peptide sequence of either synthetic peptides VIIIE or IXD, the only purported HCV sequences shown to have been subjected to EIA testing in Examples 15 to 18. Wang has a plethora of errors with regard to the stated sequence information. Sequences VIIIE and IXD originally were wrong in most occurrences and Wang later attempted to change them (see again Mueth Declaration, filed January 31, 2007, containing the Preliminary Amendment filed by Wang December 10, 1990 [Wang Paper No. 3], and the Requests for Certificate of Correction filed February 25, 1993 [Wang Paper No. 10] and August 29, 1994 [Wang Paper No. 19]). The VIII and IX series of peptides both have errors in them. First, for peptide IX (replacing Thr with Tyr and Tyr with Thr at two different locations of the peptide) was requested on February 25, 1993 with Certificate of Correction finally issued on September 20, 1994. Second, there was also an error in Peptide VIII, which is the N-terminal segment of the HCV capsid, where the amino acid no. 13 of said peptide (this equals amino acid no. 14 of the capsid sequence, since Wang's peptide VIII begins with aa no. 2) was first stated as His, then corrected (per

Preliminary Amendment dated December 10, 1990) to Asn. These are not conservative substitutions. Wang itself teaches (column 4, lines 27 et. seq.) that the conservative substitutions are shown in Table 6 ("These show where conservative substitutions, deletions or substitutions can be made."). The errors and attempted corrections made reflect non-conservative substitutions and as such are neither typographical errors, nor irrelevant (conservative) amino acid changes.

As is pointed out eloquently in the paper by P.M. Colman, "Effects of amino acid changes on antibody-antigen interactions", Research in Immunology, No. 1, 145:33-36 (1994), on file, including the many references in the article (which precede July, 1990), a single amino acid change within the interface of an antibody-antigen complex can have a profound effect on the stability of the complex, the direction of which is, even today, most difficult if not impossible to predict. The erroneous original disclosure of Wang made it impossible as of the July 26, 1990 filing date to ascertain the true antigen epitope sequence configuration which would give the results of Example 17.

It is essential to note that as of July 26, 1990, the actual sequence of the capsid portion of the HCV genome including HCV sequences VIIIE and IXD were not publicly known. Consequently, by presenting erroneous peptide sequences for both VIIIE and IXD, Wang had nothing to point to for establishing which of the alternatives were the correct ones. Wang had no acceptable basis upon which to choose the sequences of Table 7 over the alternative and contradictory sequences scattered throughout the

Wang Specification (or vice versa).

Thus, the July 26, 1990 Wang patent application filing in the sequence information was incorrect and contradictory in regard to HCV sequences VIIIE and IXD.

The Federal Circuit has held that where the invention resides is the sequence, disclosure of the sequence structure is essential to the sufficiency of disclosure in the sense of 35 U.S.C. 112, Fiers v. Sugano, 25 USPQ2d 1601 (Fed. Cir. 1993), and Regents of the Univ. of Cal. v. Eli Lilly & Co. 119 F.3d 1559, 1566, 43 USPQ2d 1398, 1404 (Fed. Cir. 1997), *cert. denied* 523 U.S. 1089 (1998).

Eli Lilly held that an adequate written description of genetic material

"requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. [emphasis added]

43 USPQ2d at 1404 (quoting Fiers at 25 USPQ2d at 1606).

The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter of the claim, 43 USPQ2d at 1406. A description of what the genetic material does, rather than of what it is, does not suffice. The holding in Eli

Lilly is fatal to the sufficiency of the disclosure of the Wang Specification as filed on July 26, 1990, because the originally disclosed sequences XIE and IXD did not represent the correct sequences. Applicant cannot be rejected over erroneous, inconsistent sequence data.

There appears to be a misunderstanding regarding applicants' position. The Certificates of Correction are, as a matter of law, without retroactive effect. In Novo Industries L.P. v. Micro Molds Corp., 350 F.3d 1348, 69 USPQ 2d 1128, 1133 (CAFC 2003) the Federal Circuit, in construing the Certificate of Correction statutory provisions (35 U.S.C. 254, 255), held:

Indeed, sections 255 and 554 themselves suggest that the[y] were not intended to address the authority of the district courts to correct patents by construction where no certificate of correction has been issued by the PTO. Those sections deal only with the authority of the PTO to make prospectively effective corrections, and the PTO was given no authority to correct the claim retroactively. Section 255 states, 'Such [corrected] patent, together with the certificate, shall have the same effect and operation in law on the trial of actions for causes thereafter arising as if the same had been originally issued in such corrected form.' 35 U.S.C. §255. Section 254 is substantially similar in this respect. As we held in Southwest Software, Inc. v. Harlequin, Inc., 266 F.3d 1280 [56 USPQ2d

1161] (Fed. Cir. 2000), under sections 254 and 255, a 'certificate of correction is only effective for causes of action arising after it was issued.' Id. at 1294. For causes of action that arise before the correction becomes effective, the patent must be considered without the benefit of the certificate of correction. [emphasis added]

See also Chisum, vol. 4, ¶ 11.07 [3], p. 11-684 et. seq.

Particularly relevant in the present context is the statement in Novo Industries with specific reference to the extent of the authority granted to the Patent and Trademark Office by Sections 254, 255:

Those sections deal only with the authority of the PTO to make prospectively effective corrections, and the PTO was given no authority to correct the claims retroactively.

This statement is applicable to the correction of the Specification as well since Sections 254 and 255 use the term "patent" and thus are not restricted to "claims".

The foregoing cases, Eli Lilly specifically, recognize that the original flawed sequences of Wang's sequences VIIIE and IXD, were erroneous and inconsistent disclosures as of the July 26, 1990 filing date, and the Certificates of Correction cannot

render obvious applicants' invention because the Certificates were without nunc pro tunc effect. The Certificates of Correction were not made to revise the sequence information regarding Wang's sequences VIIIE and IXD until well after applicants' effective filing date.

### SUMMARY

Wang is not "prior art" in light of the Declaration Under 37 CFR 1.131.

Wang taken with Houghton does not disclose or suggest the combination of capsid plus C-100-3 to, surprisingly, detect early seroconversion and reduce false negatives.

Wang's July 26, 1990 filing was erroneous in its original disclosure of the HCV sequences of VIIIE and IXD, and did not actually disclose which of those sequences were correct until long after applicant's filing date of August 27, 1990. The Certificates of Correction subsequently filed by Wang to correct the errors were without retroactive effect. Houghton is also completely devoid of any disclosure of structural HCV genes including the capsid to detect early seroconversion.

Consequently, the combination of Wang with Houghton does not result in the HCV assay methods providing early detection forming the subject matter of the present invention.

The rejection of Wang with Houghton should be withdrawn.

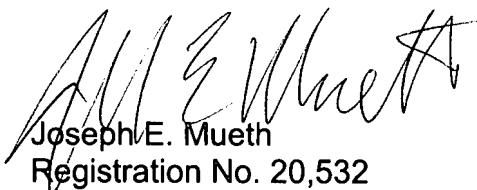
All of the rejections should be withdrawn.

The Notice of Allowance is requested.

In the event this application is not allowable, entry of the above amendments to claims 140 and 141 is requested for purposes of appeal. These are minor, formalistic amendments which reduce the issues.

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Respectfully submitted,



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